Research Article

Possible effect of dialysis membrane in polymethylmethacrylate on clinical variables associated with atherosclerosis development in chronic renal failure patients

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Abstract

Background: Chronic hemodialysis patients have higher cardiovascular morbidity compared to the general population. A number of studies have suggested that patients undergoing hemodialysis with polymethylmethacrylate (PMMA) membranes have a better outcome compared to other membranes.

Methods: We performed a retrospective, multicenter study to evaluate the impact of PMMA membranes compared to other types of membranes on clinical parameters considered important risk factors for the development of cardiovascular disease in chronic kidney disease patients.

Results: The study included 104 patients (52 patients on PMMA and 52 patients on other membranes) from ten dialysis centers, monitored for 24 months. HDL cholesterol (mg/dL) increased significantly in the PMMA group (41.4 ± 10.8 to 44.1 ± 13.5, p = 0.0467), but not in the control group (41.8 ± 13.8 to 39.4 ± 9.6, p = 0.8628). At 24 months total cholesterol and triglycerides (mg/dl) were significantly lower in the PMMA group than in the control group (142.4 ± 43.8 vs. 166.1 ± 43.4, p = 0.0321 and 106 (76.5-176) vs. 170 (118-254), p = 0.014), respectively. Serum creatinine (mg/dL) increased significantly from baseline to 24months in the PMMA group (9.20 ± 2.8 to 21.1 ± 4.6, p = 0.0001).

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2.5 to 9.47 ± 2.3, p = 0.0291), but not in the patients treated with other membranes (8.39 ± 2.6 to 8.37 ± 2.3, p = 0.2743). In addition creatinine was significantly higher in the PMMA group compared to the other group (9.47 ± 2.3 vs. 8.37 ± 2.3, p = 0.0493).

WBCs (10^9/L) increased significantly in the control group (6151 ± 1846 to 6672 ± 1872, p = 0.0457) but not in the PMMA group (6326 ± 2113 to 6152 ± 1832, p = 0.8981). At 24 months platelets (10^9/L) and CRP (ng/dL) were significantly lower in the PMMA group compared to the control group (185 (144-222) vs. 210 (173-259), p = 0.0498 and 0.70 (0.30-1.59) vs. 3.76 (0.46-10.2), p = 0.023, respectively). Iron and transferrin (µg/dL) decreased significantly in the patients treated with other membrane (62.5 ± 30.4 to 52.6 ± 19.0, p = 0.0113 and 178 (157-218) to 170 (124-203), p = 0.0019, respectively), but not in the PMMA group.

Conclusion: This retrospective study of data from 104 patients shows a favorable effect of PMMA on clinical variables considered relevant for the development of atherosclerosis in hemodialysis patients.

Introduction

In chronic hemodialysis patients, morbidity and mortality due to cardiovascular disease are considerably higher compared to the general population. Several studies have shown that traditional risk factors for cardiovascular diseases, such as diabetes, smoking, higher systolic pressure, elevated total cholesterol and decreased High-Density Lipoprotein (HDL) are important factors in the development of atherosclerosis in Chronic Kidney Disease (CKD) patients [1]. CKD patients with low HDL levels have a poor prognosis [2]. Inflammation also appears to play an important role in the pathology of atherosclerosis in these patients. C-Reactive Protein (CRP) is a well-known marker for inflammation and may play an active role in cardiovascular disease [3]. White Blood Cell (WBC) count is a traditional indicator of inflammation and infection responses and previous studies revealed the significant association of WBC count and adverse cardiovascular outcome in dialysis patients [4,5]. A 2016 study seems to confirm that platelet count is associated with an increase in vascular mortality, future cardiovascular disease, and future cancer in a cohort study population not on dialysis [6–8]. Other inflammatory markers, like the cytokines TNF-α, IL–6 and IL–10 may play a role [9]. Hyperinsulinemia and insulin resistance are common in kidney disease and have been shown to correlate with cardiovascular disease mortality in patients with end-stage renal disease [10]. Elevated level of Homocysteine (tHcy) has been associated with increased morbidity and mortality in patients with kidney failure [11]. Abnormal mineral metabolism can promote arterial calcification and arterial stiffness and hyperphosphatemia and elevated calcium phosphate product may be involved in cardiovascular disease in kidney failure [12]. Anemia correlates with cardiovascular disease mortality and morbidity [13].

A number of studies have suggested that patients undergoing hemodialysis with Polymethylmethacrylate (PMMA) membranes have a better outcome in terms of morbidity and mortality compared to other membranes [14–17]. The present study aimed to evaluate the behavior of the numerous parameters involved in the progression of atherosclerotic processes or in predicting the progression of cardiovascular events, during a period of 24 months of dialysis treatment with PMMA membranes, compared with a group of patients treated with other membrane types.

Materials and methods

Study design

The study was a retrospective multicenter study to investigate the possible effect of PMMA on clinical variables considered relevant for the development of atherosclerosis in chronic renal failure patients undergoing hemodialysis with dialyzers in Polymethylmethacrylate (PMMA) compared to other types of membranes. The primary objective of this study was to study the effect of the PMMA dialyzer on various biochemical and clinical parameters that have been identified as important risk factors for the development of cardiovascular disease in chronic kidney disease patients.

Patient characteristics and enrollment criteria

Among all patients from the participating centers, patients were enrolled in the study if they had undergone bicarbonate hemodialysis for at least two years, were aged 40–75 years and had not had any previous incidence of cancer, cardiovascular disease (especially ischemic heart disease also excluding episodes of anginal type) or serious infections (i.e. requiring hospitalization). Patients who were treated with PMMA and patients who were treated with other types of membranes were equally distributed according to age, sex, dialysis vintage, weight loss/6 months and Kt/V in order to have a balanced distribution in the two study groups.

Clinical and laboratory parameters

We collected data on biochemical and clinical parameters that have been identified as important risk factors for the development of cardiovascular disease in chronic kidney disease patients. Biochemical parameters were collected every 6 months over a period of 2 years and included variables related to nutritional condition end dialysis efficiency (total protein, albumin, Kt/V, creatinine, urea, uric acid), lipidic profile (total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides), inflammatory factors (white blood cells, platelets, CRP), iron status (ferritin, hemoglobin, iron, transferrin) and mineral metabolism (calcium, phosphate, product Ca×P).

Statistical analysis

Normality tests were performed using the Kolmogorov–Smirnov test. Quantitative normally distributed variables are presented as mean ± Standard Deviation (SD) and non-normally distributed variables as median and the 25th–75th quartiles range. Univariate comparison was performed to compare variables between two groups. In all comparisons p<0.05 was considered statistically significant. Student’s t-test, Wilcoxon test and Mann–Whitney test were used to compare means in case of normal paired or unpaired samples, non-normal paired samples and non-normal unpaired samples, respectively.
**Results**

A total of 104 patients were enrolled in the study, 52 patients underwent hemodialysis with PMMA membranes and 52 patients were treated with other types of membranes. Ten Italian dialysis centers contributed to this study. Baseline characteristics are shown in Table 1. No significant difference was present between the two patient groups. There was no change in the pharmaceutical therapies given to the patients during the observation period.

Table 2 summarizes biochemical parameters at baseline (T0) and after 24 months (T24) for patients treated with PMMA and patients treated with other membrane types. There were no significant differences between the two groups at baseline. Serum total proteins and albumin did not change after 24 months and within the two groups. Serum creatinine (mg/dL) increased significantly from baseline to T24 in the PMMA group (9.20 ± 2.5 to 9.47 ± 2.3, p = 0.0291), but not in the group patients treated with other membranes (8.39 ± 2.6 to 8.37 ± 2.3, p = 0.2743). At 24 months creatinine was significantly higher in the PMMA group compared to the other group (9.47 ± 2.3 vs. 8.37 ± 2.3, p = 0.0493). All other parameters did not change significantly between the two groups and during 24 months.

HDL cholesterol (mg/dL) increased significantly in the PMMA group (41.4 ± 10.8 to 44.1 ± 13.5, p = 0.0467), but not in the other group (41.8 ± 13.8 to 39.4 ± 9.6, p = 0.8628). At 24 months total cholesterol and triglycerides (mg/dL ) were significantly lower in the PMMA group than in the other group (162.4 ± 43.8 vs. 166.1 ± 43.4, p = 0.0321 and 106 (76.5-176) vs. 170 (118-254), p = 0.014, respectively . LDL (mg/dL ) did not change significantly between the two groups and during 24 months.

Among inflammatory markers WBCs (10^9/L) increased significantly in the group treated with other membranes (6151 ± 1846 to 6672 ± 1872, p = 0.0457) but not in the PMMA group (6326 ± 2113 to 6152 ± 1832, p = 0.8981). At 24 months platelets (10^9/L) and CRP (mg/dL) were significantly lower in the PMMA group compared to the other group (185 (144-222) vs. 210 (173-259), p = 0.0498 and 0.70 (0.30-1.59) vs. 3.76 (0.46-10.2), p = 0.023, respectively ).

Iron and transferrin (μg/dL) decreased significantly in the patients treated with other membrane (62.5 ± 30.4 to 52.6 ± 19.0, p = 0.0113 and 178 (157-218) to 170 (124-203), p = 0.0019, respectively), but not in the PMMA group. No difference within and between the two groups as regards Hb and Ferritin. There was no significant difference as regards Ca, P and calcium-phosphate product between and within any of the two groups. β2-microglobulin did not change in any period and within any group.

**Discussion**

End stage renal disease (ESRD) has become a prototype for chronic inflammation. There is consistent evidence that CRP and pro-inflammatory cytokines, such as IL-1, IL-6 and TNF-α are risk factors for atherosclerotic complications and...
predict death and adverse cardiovascular outcomes [18–20]. Levels of CRP increase as the renal function deteriorates and are particularly high in HD patients. Our study highlights the significant positive impact of the PMMA membrane, known for its high adsorption capacity and biocompatibility, in reducing CRP levels after a period of two years, compared to other membranes. It has been suggested that the rapidly developing atherosclerosis in ESRD patients could be caused by a synergism of different mechanisms such as malnutrition, inflammation, and oxidative stress [18–20]. In our study, BMI did not show any state of malnutrition among the patients of the two groups in a period of the 24 months considered. With regard to PMMA, compared to other membranes, it seems very likely that the significant increase in creatinine at 24 months depends on an increase in the weight of the patients. In this case, we advance the possibility that serum creatinine level depends not only on muscle mass but also on muscle quality, as reported by MBPajec in a work of 2018 [21]. In their work, the authors concluded that each kg of lean body mass was associated with 7.7 mol/L or 0.09 mg/dL increase in serum creatinine concentration. Thus confirming a better condition of anabolism linked to the use of PMMA, which also contributes to better control of the progression of atherosclerosis.

Some therapeutic approaches have been suggested, such as antioxidant therapy and ACE inhibitors [22] together with statins that might be able to reduce CRP levels [23,24]. We emphasize that drug therapies remained unchanged during the two years of observation in the two groups of patients. Schwarz, et al. [6] have shown that coronary atherosclerotic plaques in ESRD patients are characterized by increased medial thickness, infiltration by and activation of macrophages and marked calcification. Serum ferritin may be increased due to non-iron-related factors including elements of the malnutrition-inflammation complex syndrome. The probability of having moderately high serum ferritin ≥500 ng/ml can be explained by both iron stores and inflammation. The seemingly paradoxical combination of serum ferritin ≥500 ng/ml and transferrin saturation < 25% in HD patients is associated with an increased level of inflammatory markers [25]. Hence, in dealing with HD patients with ferritin levels >500 ng/ml, the possibility of higher levels of circulating inflammatory cytokines should be considered as an alternative explanation to iron overload [25]. The diagnostic validity and reliability of serum ferritin in diagnosing anemia and iron treatment adequacy need to be revisited in additional studies.

In our study, patients treated with PMMA membranes showed better control of ferritin and iron concentration linked to the significant reduction of inflammation markers. Concerning WBC count, even if decreased during PMMA treatment, the data is difficult to consider positive on inflammation and then atherosclerosis, because different studies regarding the WBC count as a predictor of clinical outcome are controversial [4,5,8].

Other mechanisms and factors of cardiovascular risk are platelets and their effects on blood viscosity and prothrombotic state that may predispose dialysis patients to cardiovascular events [6,8]. For example, the various mechanisms of CD40 receptor and CD40L on platelets activation are of particular interest [7]. Binding of CD40L to its CD40 receptor on endothelial cell and platelet membranes seems to induce an enhanced release of potent proinflammatory and atherosclerosis-promoting cytokines and chemokines [7]. The use of PMMA reduced the number of platelets over time, probably due to its reductive effects on the CD40 fractions. We could not dose CD40 fractions during the present study, however, we emphasize that in our previous studies and other authors, PMMA membrane demonstrated its powerful absorptive capacity with respect to soluble CD40 and CD40L inducing an improvement in the immune response, especially during Hepatitis B vaccination [26–31].

The role of hypercholesterolemia as a risk factor for the development of cardiovascular disease in moderate and severe chronic kidney disease is actively debated, mainly because of the inconsistent and often paradoxical relationships reported in observational studies [32,33]. CKD patients with low HDL levels have a poor prognosis [2]. In the present study HDL cholesterol increased significantly in the PMMA group, but not in the control group. HD significantly affects lipoprotein metabolism and dyslipidemia through membrane used (high flux vs. low flux), type of dialysate (bicarbonate vs. acetate), anticoagulant (heparin) and the phosphate-binder (sevelamer hydrochloride) [33,34]. We reiterate that dialysis modalities and drug therapies remained unchanged during the two years of observation and BMI remained unmodified.

An effect of confounding factors such as dialysis characteristics, medication, diet or heparin dosage were excluded because these factors were not different in the treatment group and the control group and did not change throughout the study. In conclusion these results establish that hemodialysis with PMMA membranes, with respect to other membranes, has a favorable effect on some of the main metabolic and nutritional parameters and some phlogistic and immunological mechanisms underlying the atherosclerotic processes, therefore its use should find an indication in HD patients at greater cardiovascular risk.

Conclusion

This retrospective study of data from 104 patients monitored over a period of 24 months from ten Italian dialysis centers, shows a favorable effect of PMMA on clinical variables considered relevant for the development of atherosclerosis in hemodialysis patients. The observed positive effect may be explained by the superior biocompatibility of PMMA compared to other membranes, as well as its adsorptive capacities. Due to the retrospective nature of this study, it was not possible to collect data on specific variables, such as cytokines and components of the CD40 system. It would be interesting to address these issues in a future prospective study.

References


